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Incremental Value of Cystatin C Over Conventional Renal Metrics for Predicting Clinical Response and Outcomes in Cardiac Resynchronization Therapy: The BIOCRT Study

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Abstract

Background—Despite the benefit of CRT in select patients with heart failure (HF), there remains significant need for predicting those at risk for adverse outcomes for this effective but costly therapy. CysC, an emerging marker of renal function, is predictive of worsening symptoms and mortality in patients with HF. This study assessed the utility of baseline and serial measures of cystatin C (CysC), compared to conventional creatinine-based measures of renal function (estimated glomerular filtration rate, eGFR), in predicting clinical outcomes following cardiac resynchronization therapy (CRT).

Methods—In 133 patients, we measured peripheral venous (PV) and coronary sinus (CS) CysC concentrations and peripheral creatinine levels at the time of CRT implant. Study endpoints included clinical response to CRT at 6 months and major adverse cardiac events (MACE) at 2 years.

Results—While all 3 renal metrics were predictive of MACE (all adjusted $p < 0.02$), only CysC was associated with CRT non-response at 6 months (adjusted odds ratio 3.6, $p=0.02$). CysC improved prediction of CRT non-response ($p < 0.003$) in net reclassification index analysis

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compared to models utilizing standard renal metrics. Serial CysC >1mg/L was associated with 6-month CRT non-response and reduced 6-minute walk distance as well as 2-year MACE (all $p < 0.04$).

Conclusion—In patients undergoing CRT, CysC demonstrated incremental benefit in the prediction of CRT non-response when compared to standard metrics of renal function. Baseline and serial measures of elevated CysC were predictive of CRT non-response and functional status at 6 months as well as long term clinical outcomes.

Keywords

cardiac resynchronization; heart failure; biomarkers; cystatin C

Introduction

Cardiac resynchronization therapy (CRT) significantly reduces morbidity and mortality in patients with symptomatic heart failure (HF), left ventricular systolic dysfunction (LVSD; left ventricular ejection fraction $< 35\%$) and electrical dyssynchrony (QRS > 120 msec).¹ Reversal of electrical dyssynchrony in the failing heart yields increased mechanical pumping efficiency, favorable ventricular reverse remodeling, and ultimately improved clinical outcomes. Despite the established benefits of CRT, nearly one-third of patients demonstrate clinical non-response, framing the important need for additional determinants of clinical outcome for this effective but nonetheless costly therapy.

Chronic kidney disease (CKD) has been increasingly identified as a determinant of poor clinical outcome following CRT.² The prognostic impact of CKD in this population is important given that nearly 40% of patients who may be candidates for CRT have abnormal renal function.³ Historically, renal function has been estimated using serum creatinine or the estimated glomerular filtration rate (eGFR), both of which may be particularly inaccurate in patients with LVSD.⁴ Cystatin C (CysC), an emerging biomarker of renal function, has demonstrated superior accuracy compared to conventional renal markers,⁴ and elevated CysC levels have been associated with worse clinical outcomes in patients with LVSD.⁵

The ability of CysC to predict clinical response and cardiac morbidity following CRT has not been definitively established. Thus, we aimed to compare the ability of CysC versus conventional markers of renal function (creatinine and eGFR) in the prediction of clinical response and major adverse cardiovascular events (MACE) in patients undergoing CRT. To better understand the mechanism and localization of CysC synthesis, we compared CysC levels in the coronary sinus (CS) and peripheral veins (PV) in a subset of patients where CS and PV samples were obtained simultaneously during device implantation.

METHODS

Study Population and Protocol

“Biomarkers to Predict CRT Response in Patients With HF” (BIOCRT; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01949246) # NCT01949246) is a prospective observational study consisting of New York Heart Association (NYHA) functional class II–IV patients undergoing CRT device implantation

between December 2007 and July 2012 from a single tertiary hospital, from whom blood from the CS and PV were drawn during the time of device implantation and serial PV blood drawn at 1 month and 6 months post-CRT implant. Enrollment was performed consecutively. Details on the study design as well as inclusion and exclusion criteria have been previously reported.⁶ Briefly, eligible patients were CRT candidates with symptomatic HF (NYHA functional class II–IV, refractory to optimal medical therapy), LVEF $\geq 35\%$, QRS duration ≥ 120 ms, and recent HF episode within the prior year. Major exclusion criteria include co-morbidities limiting lifespan to < 6 months, severe aortic stenosis, recent cardiac surgery or revascularization within 90 days, chronic obstructive pulmonary disease, primary pulmonary hypertension, or requirement of continuous infusion HF therapy. In addition to serial blood draws, participants underwent serial medical history (including NYHA functional class and global assessment score), six-minute walk tests (6MWT), 12-lead electrocardiograms, and transthoracic echocardiograms (echo) at baseline, 1 month, and 6 months. Invasive coronary venography was used to guide LV pacing lead placement and echo-guided optimization of the CRT device occurred at 1 month. Study participants were followed for events through a time horizon of up to 2 years. The Social Security Death Index and medical chart were reviewed between April 11, 2013 and August 1, 2014 for clinical outcome determination. Clinical outcome events occurring outside the implanting institution were solicited from patients and confirmed via review of the medical chart. Our institutional review board approved the study protocol, and all patients provided written informed consent.

For this analysis, we included 133 patients who had both PV CysC and creatinine measurements. We also analyzed the subset of 93 patients with simultaneously drawn CS and PV samples during device implantation.

Blood Samples

At the time of device implantation baseline CS blood was drawn from the CS guiding catheter prior to delivering the left ventricular pacing lead. PV blood was drawn simultaneously from an upper extremity vein. Serial PV blood samples were also collected at 1-month and 6-month follow-up visits. Blood was collected in tubes containing heparin and in tubes without anticoagulant. For creatinine, PV samples were immediately sent to the Massachusetts General Hospital core laboratory for routine analysis. Plasma creatinine measurements (Creatinine Jaffé Gen.2; Roche Diagnostics) were performed by kinetic colorimetric assay based on the Jaffé method, with an interassay coefficients of variation (CV) of 1.3% and intraassay CV of 2.5% . Using the creatinine value, we calculated eGFR using the Modification of Diet in Renal Disease (MDRD) equation.⁷

For CysC analysis, samples were immediately centrifuged, and the aliquoted serum was stored in microcentrifuge tubes at -80°C until assayed. Anonymized specimens were sent to an independent laboratory (Siemens Healthcare Diagnostics Inc.) for analysis. In addition to being blinded to the clinical history, the laboratory was blinded to the knowledge of whether the samples were CS or PV as well as if samples were baseline, 1-month or 6-month draws. All analyses were performed on a first freeze thaw cycle. Serum CysC measurements

(Dimension Vista; Siemens) were performed by nephelometry, with an interassay coefficients of variation (CV) of <3% and intraassay CV of <5%.

End Points

CRT response was assessed at 6 months using the HF Clinical Composite Score (CCS)⁸ by an adjudicating committee. An outcome panel consisting of two cardiologists, blinded to the biomarker results, determined the clinical response of each subject based on review of the medical record, with disagreement resolved by consensus with a third cardiologist. The HF CCS includes both subjective (global assessment score as self-assessed by patient and change in NYHA functional class deemed by physician) and objective (mortality and HF hospitalization) metrics.⁸ A patient's CCS was classified as one of the following: worsened (the patient died or was hospitalized for or associated with worsening HF, demonstrated worsening in NYHA class, had moderate or marked worsening of patient global assessment score, or permanently discontinued CRT because of or associated with worsening heart failure), improved (the patient had not worsened as defined above and demonstrated improvement in NYHA class or had moderate or marked improvement in patient global assessment score), or unchanged (the patient was neither improved nor worsened). Responders were defined as those with improved CCS from baseline to 6 month follow-up. Those not meeting this criterion (including unchanged CCS) were considered nonresponders. MACE was defined as the composite endpoint of death, cardiac transplant, left ventricular assist device (LVAD) implantation, and HF hospitalization within 2 years.

Statistical Analysis

Descriptive statistics were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range for continuous variables and as frequencies and percentages for nominal variables. Comparisons of continuous variables were made with a t-test or the Wilcoxon rank-sum test as appropriate; comparisons of nominal variables were made using a chi-squared test. Correlation between CS and PV samples was performed using Spearman correlation. The association between renal markers and outcomes was performed using logistic regression for CRT response and Cox proportional hazards for 2-year MACE. Adjustment was made for standard covariates associated with CRT response: age, sex, presence of ischemic cardiomyopathy, presence of left bundle branch block (LBBB), and QRS duration. Model discrimination was performed using the C-statistic and model comparison was performed using nested models (eg. log-CysC beyond log-creatinine or eGFR). The incremental value of CysC for predicting outcome was performed using continuous net reclassification index (NRI) analysis with 999 bootstrap replications to estimate 95% confidence intervals.⁹ Optimal cut-point analysis was performed using receiver operating characteristic (ROC) curves and Youden's index. Cumulative event rates were estimated using Kaplan-Meier analysis; strata were compared using the log-rank test. Serial CysC models were landmarked for the relevant draw time (i.e. 1-month or 6-months). A 2-tailed p-value of <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (Cary, North Carolina).

RESULTS

Patient Characteristics

Table 1 depicts the baseline clinical characteristics of all patients and as stratified by CRT response. This advanced LVSD population (mean LVEF 25%) was predominantly male and significantly symptomatic despite optimal medical therapy (86% NYHA class III). LBBB was present in half of patients with two-thirds of patients demonstrating marked conduction delay reflected by a QRS >150 ms. Compared to non-responders, CRT responders were less likely to have ischemic cardiomyopathy, more likely to have LBBB at baseline, and had smaller left ventricular end-systolic volumes (all $p < 0.04$).

Metrics of Renal Function Levels: Cystatin C, Creatinine, eGFR

Table 1 shows the baseline concentrations of CysC, creatinine, and eGFR in the entire study cohort as well as stratified by CRT responder status. CysC levels were commensurate with those reported in similarly advanced LVSD populations.^{10–12} CysC was positively correlated with creatinine ($\rho=0.55$, $p<0.001$) and inversely correlated with eGFR ($\rho=-0.57$, $p<0.001$).

Clinical Follow-up and Outcomes

There were 53 (40%) patients adjudicated as CRT non-responders at 6 months, utilizing HF CCS criteria. For the entire study population, at 2-year follow-up, there were 32 (24%) patients who experienced at least one component of the composite MACE endpoint, including 29 (22%) patients with a HF hospitalization, 2 (2%) requiring LVAD, 2 (2%) undergoing heart transplantation, and 13 (10%) deaths.

Association of Renal Markers to CRT Response and MACE

All renal markers were associated with CRT non-response at 6 months in univariate analysis (Table 2). However, after adjustment for standard predictors of clinical outcome in CRT (age, sex, ischemic cardiomyopathy, LBBB) only PV log-CysC remained associated with CRT non-response (OR 3.6, $p=0.02$) (Table 2). Neither log-creatinine nor eGFR were predictive of CRT non-response following adjustment (both $p > 0.19$). Moreover, log-CysC remained the only renal metric significantly predictive of non-response in these adjusted models with the addition of either log-creatinine (OR 3.6, 95% CI 1.1–12.1, $p=0.04$) or eGFR (OR 3.9, 95% CI 1.2–12.9, $p=0.03$).

With respect to long-term clinical outcome, all 3 renal markers remained associated with 2-year MACE after adjustment for standard predictors (all $p < 0.02$, Table 2).

Incremental Value of Cystatin C Beyond Standard Renal Markers for Predicting CRT Non-Response

The C -statistics increased from 0.60–0.62 to 0.68 with the addition of log-CysC to models of CRT non-response employing conventional renal markers, although these increases were not significantly different (p both > 0.09). However, the addition of log-CysC significantly improved the classification of non-response risk prediction when added to baseline models with logcreatinine ($p=0.003$) or with eGFR ($p=0.002$) (Table 3). When compared to a

reference model of standard renal markers, the addition of log-CysC correctly reclassified risk prediction of CRT non-response in more than half of the cohort (52–56%). In contrast, there was no significant difference in risk reclassification ($p = 0.27$) when adding log-CysC to a reference model of standard renal metrics predicting 2-year MACE (Table 3).

Association of Cystatin C >1 mg/L with CRT Response and MACE

The optimal cutpoint of CysC for predicting CRT non-response was 0.98 mg/L (C -statistic = 0.67). For simplicity, we used a CysC cutpoint of 1 mg/L in our analyses (C -statistic = 0.67). Compared to patients with CysC ≤ 1 mg/L ($n=77$), patients with baseline CysC >1 mg/L ($n=56$) had a 4-fold increase in the odds of CRT non-response (OR 4.1, $p<0.001$) and an increased hazard for 2-year MACE (Table 4, Figure 1, Supplementary Table 1).

Serial Cystatin C measurement

At 1 month post-CRT, the median CysC level was 1.0 mg/L [IQR 0.76 – 1.4 mg/L] ($n=92$) and similar to the median CysC level at 6 months post-implant (1.0 mg/L [IQR 0.75 – 1.4 mg/L]) ($n=84$). Among patients with serial PV CysC measurements, log-CysC values at 1-month and 6-months were associated with CRT non-response (adjusted $p = 0.06$) and 2-year MACE (adjusted $p = 0.05$) (Table 4).

For patients with serial CysC measurements, the association between CysC and clinical outcome was assessed statically at serial timepoints (Figure 2). When assessed statically, there was a greater proportion of patients with CysC >1 mg/L (measured at baseline, 1-month, and 6-months) who were CRT non-responders at 6 months ($p<0.006$) and who developed MACE at 2 years ($p<0.04$). Compared to patients with CysC ≤ 1 mg/L, patients with CysC >1 mg/L incurred a greater than 3-fold increase in adjusted risk for both CRT non-response and 2-year MACE, irrespective of baseline, 1-month, or 6-month assessment (Table 4).

Cystatin C and Functional Capacity

CysC was inversely correlated with 6MWT distance at baseline and during longitudinal assessment (baseline $\rho = -0.44$, 1-month $\rho = -0.45$, 6-month $\rho = -0.45$; all $p<0.001$). Patients with baseline CysC >1 mg/L had significantly reduced 6MWT distance at baseline compared to those with CysC ≤ 1 mg/L (766 $\pm$ 400 feet vs 1056 $\pm$ 378 feet, $p<0.001$) which persisted at six-month follow-up (925 $\pm$ 370 feet vs 1225 $\pm$ 400 feet, $p<0.001$) (Figure 3). Similar to the baseline CysC results, both patients with CysC >1mg/L at 1-month and 6-month assessment had significantly decreased 6MWT distances as compared to those with CysC ≤ 1 mg/L (1-month: 927 $\pm$ 374 feet vs. 1252 $\pm$ 353 feet; 6-month: 923 $\pm$ 386 feet vs. 1275 $\pm$ 374 feet; both $p<0.001$).

Coronary Sinus Cystatin C Levels

For the 93 patients with both CS and PV samples, median levels of CysC in the PV were 0.94 [0.78, 1.30] mg/L and higher than median CS levels of 0.84 [0.66, 1.10] mg/L ($p<0.001$). While there was strong correlation between CS and PV CysC ($\rho=0.71$, $p<0.001$), CysC levels in the CS were approximately 10% lower, with trans-cardiac gradient (CS-PV) of -0.08 [-0.19 , 0.02] mg/L, and trans-cardiac ratio (CS/PV) of 0.90 [0.83, 1.02].

Similar to PV results, elevated CS CysC was associated with increased CRT nonresponse and an increased risk of 2-year MACE (adjusted p for both = 0.04, Table 2). Neither CS-PV gradient nor CS-PV ratio were associated with CRT response or 2-year MACE (Table 2, all p = 0.12).

DISCUSSION

In this prospective, cohort study utilizing serial assessment of the novel renal biomarker CysC, we identified the following central findings: (a) increased baseline CysC, but not standard metrics of renal function (creatinine, eGFR), independently predicted CRT non-response even after accounting for established covariates. Furthermore, CysC significantly improved risk prediction of CRT non-response over standard renal markers as reflected by net reclassification index analysis. (b) Elevated CysC was significantly associated with CRT non-response and adverse 2-year clinical outcome when assessed statically at serial timepoints. (c) Elevated baseline cystatin C was predictive of worse functional status at baseline and short-term follow-up. (d) Consistent with the peripheral synthesis of CysC, there was no clinically significant transcoronary gradient of CysC.

Cystatin C in Predicting CRT Response and Superiority to Conventional Renal Markers

The prognostic influence of CKD on survival in patients undergoing CRT has been conflicting. Although observational studies suggest increased mortality in those with CKD undergoing CRT (pooled HR: 2.3, 95% CI: 1.6 to 3.2), subset analyses of randomized controlled trials suggest that the overall survival benefit of CRT accrues similarly to those with and without CKD.² Unfortunately, creatinine-based estimates of glomerular filtration rate rely on assumptions of physiological steady-state that are often not present in LVSD. Cystatin C, a stably expressed protease inhibitor synthesized by all nucleated cells, is not subject to variability in renal filtration, is less sensitive to clinical factors (nutrition, muscle mass, age) and therefore has been identified as a more accurate estimator of GFR.¹³ Consistent with its pattern of expression, our finding that CS cystatin C levels were approximately 10% lower than matched PV levels likely reflects the preponderance of its peripheral synthesis.

The only previous study to assess the prognostic value of CysC assessment in CRT identified elevated CysC as an independent predictor of mortality and MACE at long-term follow-up (median 3.2 years).¹⁴ Similar to this previous report, we demonstrate that CysC as well as conventional metrics of renal function were significantly associated with long-term clinical outcome. The novel contributions of this study include (a) serial assessment of CysC (baseline, 1-month, 6-months), (b) comprehensive phenotyping of clinical outcomes stratified by short-term (HF clinical composite score at 6 months) and long-term (MACE) events, and (c) careful assessment of the incremental risk prediction of CysC when compared to conventional markers. The addition of baseline CysC to models utilizing eGFR or creatinine correctly reclassified risk of CRT response or non-response in more than half of patients (NRI 52%) suggesting a significant and clinically relevant utility for CysC when compared to conventional renal markers.

Possible mechanisms by which reduced renal function is associated with CRT non-response include abnormal activation of neurohormonal (i.e. renin-angiotensin) and sympathetic nervous systems with secondary effects on sodium homeostasis, volume expansion, ventricular hypertrophy, myocardial fibrosis, and adverse ventricular remodeling.² Others have demonstrated an association between the uremia and hyperphosphatemia of CKD with myocardial vascular remodeling and structural alterations.¹⁵ Cystatin C may therefore serve as an integrative risk marker of intersecting cardio-renal pathways in patients with LVSD, including those undergoing CRT.

Serial Cystatin C: Association with Functional Status and Predicting Clinical Outcomes

In addition to the predictive value of baseline CysC assessment, we also demonstrate that elevated serial CysC was significantly associated with CRT non-response at 6 months and MACE at 2 years. For example, the presence of CysC >1 mg/L at 1-month post-implant was associated with a greater than 5-fold odds of CRT non-response, and increasing CysC measured 6 months post-implant was significantly associated with subsequent MACE over the following 18 months. Complementary to the relationship between CysC and clinical outcomes, patients with an elevated CysC demonstrated significantly worse functional status (as reflected by 6 minute walk distance) at baseline and during serial assessment post-implant (1-month, 6-months). Baseline elevated CysC was further correlated with worse functional capacity at follow-up suggesting the possible role of CysC in predicting functional capacity subsequent to CRT implantation. Of interest, elevated CysC has been associated with incident decline in exercise capacity in elderly patients,¹⁶ with proposed mechanisms including nephro-mediated metabolic disturbances such as metabolic acidosis leading to increased muscle catabolism, decreased production of vitamin D and secondary hyperparathyroidism impairing neuromuscular and skeletal function, and decreased production of erythropoietin leading to anemia and resultant fatigue.¹⁷ Baseline and serial measures of CysC (at discrete timepoints) may therefore identify patients at increased risk of poor functional status following CRT implant, which we have recently shown is linked to poor long-term clinical outcome following CRT.¹⁸

Clinical Implications

Despite the established benefits of CRT, nearly one-third of patients undergoing CRT do not demonstrate clinical response at six months.¹ To date, the most significant predictors of clinical response to CRT remain demographic, clinical, and electrical characteristics.¹⁹ In this study, CysC values > 1mg/L identified incident risk at multiple sampling intervals (baseline, 1-month, 6-months) even after accounting for standard covariates known to influence outcome in CRT. An elevated CysC may therefore be of clinical utility in both the pre-implant and post-implant risk assessment of patients undergoing CRT. In addition, early persistence of an elevated CysC may represent a subgroup of patients at particularly high risk of non-response and MACE. Identification of patients at increased risk for poor clinical outcomes may justify closer follow-up within a multidisciplinary care infrastructure – a strategy shown to be of benefit in patients undergoing CRT²⁰ – with particular focus on pacing and medical therapy optimization. Further understanding the mechanisms of association between elevated CysC and functional status may offer additional insights into the pathophysiology of functional limitation in heart failure and frame the role of targeted

therapies in this population. Finally, whether an elevated baseline cystatin C identifies a higher-risk HF population or whether an elevated cystatin C attenuates the clinical benefit of CRT warrant further exploration.

Limitations

This study has several limitations. First, the study population was characterized by relatively advanced LVSD (primarily NYHA Class III) and as such, these findings may not be generalizable to patients with less severe heart failure undergoing CRT. Second, the study enrolled patients at a single, tertiary care center. Third, the overall prevalence of LBBB in this cohort (53%) was generally low and reflects a combination of 'real-world' practice and the strict application of guideline-defined criteria of LBBB.²¹ Given the size of the cohort the study was not powered to explore differences in the utility of CysC in particular subgroups of interest, including patients with and without LBBB. Fourth, given the total number of MACE events in the study cohort, more comprehensive adjustment for covariates predictive of long-term clinical outcome (eg. 6-month echocardiographic reverse remodeling) was not possible. Fifth, additional measures of echocardiographic predictors of CRT response (eg. strain, contractile reserve) were not assessed.²² The relationship of these metrics to cystatin C may warrant future exploration. Finally, the cost-effectiveness of utilizing cystatin C in the identification of high-risk patients will need to be assessed in future analyses pending the availability of point of care testing.

CONCLUSION

In patients undergoing CRT, baseline CysC demonstrated incremental benefit in the prediction of CRT non-response when compared to standard metrics of renal function. Baseline and serial measures of elevated CysC were predictive of both CRT non-response and functional status at 6 months as well as long term clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Kaplan-Meier estimates of the probability of survival free of major adverse cardiac events (death, heart transplantation, left ventricular assist device placement, or HF hospitalization) assessed at 2 years, stratified by the optimal cystatin C cutpoint (measured at the time of CRT implant) for predicting 6-month CRT non-response.

Figure 2.

Proportion of patients with cystatin C >1 mg/L measured statically at baseline, 1-month, and 6-months in patients with and without 6-month CRT response (Panel A) and with and without 2-year MACE (Panel B).

Figure 3.

Average 6 minute walk test distance achieved at baseline and 6 months as stratified by the optimal cutpoint of baseline cystatin C ($>$ vs. ≤ 1 mg/L).

Table 1

Baseline characteristics of the BIOCRT patients and as stratified by CRT response

	All Patients (n=133)	CRT responders (n=80)	CRT non-responders (n=53)	p-value
Patient characteristics				
Age, years	65 ± 13	64 ± 14	68 ± 12	0.14
Male, n (%)	103 (77%)	58 (73%)	45 (85%)	0.09
BMI, kg/m ²	28.8 ± 5.9	29.3 ± 6.4	28.0 ± 4.9	0.22
Diabetes (%)	43 (32%)	21 (26%)	22 (42%)	0.07
History of atrial fibrillation (%)	87 (65%)	48 (60%)	39 (74%)	0.11
Hypertension (%)	47 (35%)	28 (35%)	19 (36%)	0.92
Ischemic cardiomyopathy, n (%)	60 (45%)	30 (38%)	30 (57%)	0.03
Device, n (%)	63 (47%)	33 (41%)	30 (57%)	0.08
PPM, n (%)	28 (21%)	17 (21%)	11 (21%)	0.95
ICD, n (%)	40 (30%)	19 (24%)	21 (40%)	0.05
NYHA Functional Class				0.38
I, n (%)	0 (0%)	0 (0.0%)	0 (0.0%)	
II, n (%)	12 (9%)	5 (6%)	7 (13%)	
III, n (%)	114 (86%)	71 (89%)	43 (81%)	
IV, n (%)	7 (5%)	4 (5%)	3 (6%)	
Medications				
ACEI/ARB, n (%)	107 (80%)	64 (80%)	43 (81%)	0.87
BB, n (%)	115 (86%)	68 (85%)	47 (89%)	0.54
Spironolactone, n (%)	39 (29%)	20 (25%)	19 (36%)	0.18
Diuretics, n (%)	104 (78%)	61 (76%)	43 (81%)	0.50
ECG parameters				
QRS duration, ms	162 ± 26	164 ± 26	160 ± 26	0.36
QRS >150ms (%)	88 (67%)	56 (71%)	32 (62%)	0.26
LBbB (%)	70 (53%)	48 (60%)	22 (42%)	0.04
Paced rhythm (%)	30 (23%)	18 (23%)	12 (23%)	0.98
Echocardiography parameters				
LVEF, %	25 ± 7	26 ± 7	24 ± 8	0.07
LV dimensions, mm				
End-diastole (EDD)	63 ± 9	62 ± 9	63 ± 10	0.47
End-systole (ESD)	54 ± 10	54 ± 10	55 ± 10	0.28
LV volumes, cm ³				
End-diastole (EDV)	236 ± 85	226 ± 80	253 ± 92	0.10
End-systole (ESV)	175 ± 77	164 ± 68	194 ± 87	0.04
Renal Markers				
Serum creatinine (mg/dL)	1.2 [1.0, 1.5]	1.1 [1.0, 1.4]	1.3 [1.1, 1.8]	0.02
eGFR (mL/min/1.73 m ²)	61.4±20.5	64.4±19.6	56.9±21.3	0.04
Cystatin C (mg/L)	0.9 [0.8, 1.3]	0.8 [0.7, 1.0]	1.1 [0.9, 1.4]	<0.001

BMI denotes body mass index; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; ARB, aldosterone receptor blocker; BB, beta blocker; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate. Device indicates presence of ICD and/or PPM at the time of cardiac resynchronization therapy implantation.

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Table 2

Association of Renal Metrics and Clinical Outcomes

CRT non-response at 6 months	Unadjusted OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
log-creatinine	4.5 (1.4 – 14.0)	0.01	2.4 (0.64 – 9.2)	0.19
eGFR	0.98 (0.96 – 1.00)	0.04	1.0 (0.97 – 1.0)	0.30
log-CysC	4.8 (1.8 – 12.7)	0.002	3.6 (1.2 – 10.5)	0.02
CS log-CysC	5.0 (1.6, 15.9)	0.006	4.4 (1.2 – 15.8)	0.02
log-CysC CS-PV gradient	2.1 (0.53, 8.4)	0.29	4.7 (0.65 – 33.7)	0.13
log-CysC CS/PV ratio	1.5 (0.42, 5.6)	0.52	3.3 (0.62 – 17.5)	0.16
Two-year MACE	Unadjusted HR (95% CI)	p-value	Adjusted HR† (95% CI)	p-value
log-creatinine	4.9 (1.8 – 13.6)	0.002	4.2 (1.3 – 13.7)	0.02
eGFR	0.98 (0.96 – 1.00)	0.01	0.98 (0.96 – 1.0)	0.01
log-CysC	3.3 (1.4 – 7.5)	0.006	3.5 (1.4 – 8.6)	0.007
CS log-CysC	3.4 (1.2, 9.7)	0.02	3.5 (1.2 – 10.1)	0.02
log-CysC CS-PV gradient	1.8 (0.39, 8.0)	0.46	1.7 (0.36 – 8.1)	0.51
log-CysC CS/PV ratio	1.1 (0.32, 3.8)	0.87	1.0 (0.28 – 3.9)	0.95

Renal markers were drawn from the peripheral vein unless noted otherwise.

CRT, cardiac resynchronization therapy; OR, odds ratio; CI, confidence interval; CysC, Cystatin C; eGFR, estimated glomerular filtration rate; CS, coronary sinus; PV, peripheral venous; MACE, major adverse cardiac event; HR, hazard ratio.

* Adjustment is made for age, gender, ischemic cardiomyopathy, left bundle branch block, and QRS duration.

† Adjustment is made for age, gender, ischemic cardiomyopathy, left bundle branch block, and QRS duration.

Table 3

Net reclassification index for adding Cystatin C to a model with creatinine or eGFR

	NRI (95% CI)	p-value	% events correctly reclassified	% nonevents correctly reclassified
CRT non-response				
log-creatinine + log-CysC	52% (18% – 86%)	0.003	25%	28%
eGFR + log-CysC	56% (22% – 89%)	0.002	28%	28%
Two-year MACE				
log-creatinine + log-CysC	11% (–29% – 50%)	0.29	6%	5%
eGFR + log-CysC	15% (–26% – 52%)	0.27	6%	9%

NRI, net reclassification index; CI, confidence interval; CRT, cardiac resynchronization therapy; MACE, major adverse cardiac events; CysC, Cystatin C; eGFR, estimated glomerular filtration rate.

Table 4

Association of Serial Cystatin C Measurements with Clinical Outcomes

CRT non-response at 6 months	Unadjusted OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Baseline CysC > 1mg/L	4.1 (2.0 – 8.5)	<0.001	3.2 (1.5 – 7.2)	0.004
1-month CysC > 1mg/L	5.9 (2.3 – 15.1)	<0.001	5.3 (1.9 – 14.6)	0.001
6-month CysC > 1mg/L	3.7 (1.4 – 9.6)	0.007	4.0 (1.2 – 13.6)	0.03
log-(1-month CysC)	4.3 (1.4 – 13.5)	0.01	3.1 (0.93 – 10.3)	0.06
log-(6-month CysC)	5.6 (1.7 – 18.0)	0.004	6.3 (1.4 – 27.2)	0.01
Two-year MACE	Unadjusted HR (95% CI)	p-value	Adjusted HR[‡] (95% CI)	p-value
Baseline CysC > 1mg/L	3.1 (1.5 – 6.5)	0.002	3.0 (1.4 – 6.5)	0.006
1-month CysC > 1mg/L	3.5 (1.4 – 8.8)	0.007	3.5 (1.4 – 9.0)	0.009
6-month CysC > 1mg/L [‡]	2.8 (1.0 – 7.9)	0.05	3.2 (0.95 – 10.7)	0.06
log-(1-month CysC) [‡]	4.5 (1.6 – 12.8)	0.005	3.9 (1.3 – 11.6)	0.02
log-(6-month CysC)	2.9 (1.0 – 8.4)	0.05	3.7 (1.0 – 13.6)	0.05

CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiac event; OR, odds ratio; HR, hazard ratio.

* Adjustment is made for age, sex, ischemic cardiomyopathy, left bundle branch block, and QRS duration.

[‡] Models were landmarked at 1-month or 6-months, as appropriate.

[‡] Adjustment is made for age, gender, ischemic cardiomyopathy and QRS duration.